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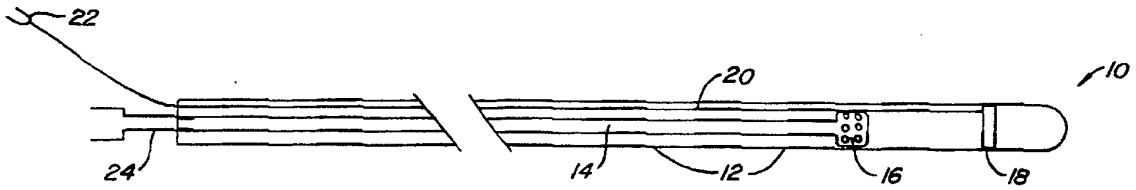

(57) Abstract

The present invention provides devices and methods for *in vivo* and *ex vivo* monitoring and normalizing of physiological parameters, such as pH, sodium, potassium, calcium, pCO_2, and pO_2. The *in vivo* devices include an elongated catheter (12) with a physiological sensor (18) mounted thereon and having a port (16) through which a physiological solution, from a device (42) for normalizing the parameter, is infused into the body. In use, the value of the parameter is measured, compared to a reference value to obtain a difference. The device for normalizing the value of the parameter then acts to reduce the difference. The *ex vivo* device functions in a similar manner, except that the blood is removed from the body and passed through the lumen of a flow through sensor containing a physiological sensor (18). Additionally, multiple sensors may be used and/or multiple parameters may be measured.

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DEVICE AND METHODS FOR MONITORING AND NORMALIZING PHYSIOLOGICAL PARAMETERS

BACKGROUND OF THE INVENTION

The present invention relates generally to devices and methods for monitoring and normalizing physiological parameters, such as blood pH, blood pO_2, and blood pCO_2. More specifically, the present invention provides devices and methods for real time monitoring of physiological parameters as well as automated normalization of such parameters.

Many disease states are caused or exacerbated by abnormal variations of correctable physiological parameters. Prompt correction of these parameters may lessen the associated morbidity or mortality. Unfortunately, overcorrection of many physiological parameters may also be associated with significant morbidity or mortality. Therefore, in many instances it is critical that the abnormal physiological parameter be corrected both accurately and rapidly.

A common example of exacerbation of an underlying disease by variations of a physiological parameter is cardiac arrest. Cardiac arrest is associated with cardiac arrhythmias, most commonly ventricular fibrillation and asystole. During cardiac arrest, tissue perfusion, even during properly performed CPR, is sufficiently low to cause peripheral hypoxia. In response to hypoxia, the peripheral cells convert to anaerobic metabolism. This, in turn, results in lactic acid production and systemic acidosis.

Cardiac arrhythmias associated with cardiac arrest are exacerbated by acidosis. Gerst et al., Circulation Res., 19:63-70 (1967). Because acidosis develops during cardiac arrest, conversion of the arrhythmias to a rhythm capable of providing adequate perfusion becomes more difficult as the time of arrest increases. Also, because most cardiac arrests occur away from a medical facility, a period of time elapses

before cardioversion can be accomplished thereby allowing acidosis to develop.

To counter the effects of acidosis on cardiac rhythm, sodium bicarbonate may be given during resuscitation. Bleich, New England Journal of Medicine, 321:1345-1346 (1989). Bicarbonate administration is also used during trauma resuscitation. Baumgartner et al., Resuscitation, 20:17-23 (1990). Generally, sodium bicarbonate is given to patients following a period of arrest. Journal of the American Medical Association, vol. 268, no. 2, October 28, 1992.

Administration of sodium bicarbonate may cause detrimental effects to the heart and other organs following cardioversion and circulatory restoration. The increased pCO_2 resulting from the buffering effect of sodium bicarbonate may lower pO_2 and increase intracellular pCO_2 concentration. Bersin et al., Am. J. Med., 87:7-14 (1989) and Jaffe, Circulation, 80:1079-1083 (1989). Therefore, it is as important to avoid administering excess sodium bicarbonate as it is to administer sufficient sodium bicarbonate during periods of arrest or hypoperfusion.

Generally, cardiopulmonary bypass, such as performed during open heart surgery, provides a relatively low blood flow to the patient. During bypass surgery, the low blood flow and attendant hypoperfusion can lead to mild tissue hypoxia and acidosis. Most commonly, the heart is in ventricular fibrillation when warmed following the procedure. The acidosis can impair cardioversion. Real time measurement and correction of acidosis during bypass could facilitate cardioversion following the procedure.

Arterial oxygen or carbon dioxide content are physiological parameters which also need to be controlled. Low oxygen tension can lead to tissue hypoxia and damage to organs such as the heart, brain, and kidneys. High inspired and blood oxygen tension can cause pulmonary damage, such as bronchopulmonary dysplasia, and eye injury, such as retrolental fibroplasia, respectively. Alterations in blood carbon dioxide tension can cause pH abnormalities and organ dysfunction as described above. Further, low blood pH may

cause neurological symptoms, such as peripheral paresthesias while high blood pH may cause hypersomnolence.

A wide variety of other physiological parameters require maintenance in a relatively narrow range. These include blood potassium, blood calcium, blood glucose, and the like. Abnormalities of these electrolytes and other compounds may cause life-threatening cardiac arrhythmias, neurological aberrations, and other undesirable physiological effects.

Devices have been developed that automatically sense and alter physiological variables. For example, Merki et al., U.S. Patent No. 5,002,055, describes regulation of gastric pH by administration of drugs that effect gastric H^+ concentration. Lee, U.S. Patent No. 4,717,548, describes a real-time blood gas analyzing system for use with extracorporeal perfusion that indirectly compensates for abnormalities by automatically altering blood flow rate by varying the speed to the perfusion pump.

What is needed in the art are *in vivo* and *ex vivo* devices and methods which can monitor physiological parameters in real time and directly normalize the chosen parameters when significant abnormalities exist. This would provide for continuous or frequent monitoring and correction without relying on medical personnel dedicated to the task. Quite surprisingly, the present invention fulfills these and other related needs.

SUMMARY OF THE INVENTION

The present invention provides devices for *in vivo* monitoring and normalizing values of blood parameters, such as blood pH, blood pCO_2, and blood pO_2, comprising an *in vivo* means for sensing the value of the blood parameter, a means for comparing the value of the blood parameter to reference values to produce value differences, and a means for decreasing the magnitude of the value differences. A plurality of physiological parameter values may be monitored and normalized together or individually. The values may also be displayed in real time or stored for future reference.

Similar devices for *ex vivo* monitoring and normalizing values of blood physiological parameters are also provided.

In related aspects, the present invention comprises an elongate body having a proximal end, a distal end, and a wall surface; a sensor located distally on the elongate body, which sensor is capable of producing a sensor signal representing the value of the physiological parameter; a sensor linkage connecting the sensor to a signal analyzer; and an analyzer linkage connecting the signal analyzer to a means for normalizing the physiological parameter. The elongate body may also contain at least one lumen for administration of physiological normalizers.

Methods for *in vivo* monitoring and normalizing a value of a physiological parameter are also provided. The methods comprise inserting the distal end of the elongate body of a device as described above into a body lumen and supplying a physiological normalizer to the pump of the device. *Ex vivo* monitoring and normalization of values of physiological parameters are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates a catheter for monitoring and normalizing pH built in accordance with the principles of the present invention.

Fig. 2 illustrates a catheter of the present invention.

Fig. 3 illustrates a multi-lumen catheter of the present invention.

Fig. 4 illustrates a catheter having two pH sensors constructed in accordance with the principles of the present invention.

Fig. 5 illustrates a catheter of the present invention having multiple lumens and multiple sensors.

Fig. 6 illustrates a device for in vivo monitoring and normalizing pH according to the principles of the present invention.

Fig. 7 illustrates a device for in vivo monitoring and normalizing blood pCO_2.

Fig. 8 illustrates a hard wired circuit for control of an infusion pump.

Figs. 9A-9F illustrate different configurations of catheters built in accordance with the principles of the present invention.

Fig. 10 illustrates a flow-through device of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention provides devices and methods for monitoring and normalizing physiological parameters in patients. The devices and methods provide means for real time monitoring and direct and indirect normalizing the parameters. The monitoring can be performed continuously or at regulated intervals. The monitoring and normalization may occur *in vivo* or *ex vivo*. As used herein, "in vivo" will be understood to mean that the physiological parameter is measured within the body. Sites for measurement within the body include, e.g., blood vessels and airways. As used herein, "ex vivo" will be understood to mean that the physiological parameter is measured outside of the body, e.g., measuring blood physiological parameter values in extracorporeal perfusion.

A wide variety of physiological parameters may be monitored and normalized by the devices and methods of the present invention. Generally, the physiological parameter will be a blood physiological parameter. Such blood physiological parameters include, e.g., blood pH, blood pCO_2, blood pO_2, blood potassium concentration, blood calcium concentration, blood glucose concentration, blood magnesium concentration, and the like.

One aspect of the present invention is a catheter for sensing the value of blood pH or pCO_2. The catheter may also deliver a solution to correct the blood pH. Generally, the catheter comprises a tubular elongate body having a proximal end, a distal end, and a wall defining an interior region and an exterior region of the elongate body; a first pH sensor located distally on the exterior wall of the elongate body; and a port located distally on the elongate body, which

port provides a fluid opening between the interior region and the exterior region of the elongate body.

By "monitoring" blood pH is meant assessing the value of blood pH. The pH may be assessed continuously or intermittently. When assessed intermittently, the pH will generally be assessed about every 0.1 seconds, although this is not critical and may vary.

By "normalizing" blood pH is meant providing a treatment to the patient which acts to directly or indirectly change the acidity of the blood so that the value of the blood pH becomes closer to a predetermined reference value. Generally, the reference blood pH value will be 7.40. In some instances, a higher or lower value may be chosen. For instance, persons having chronic obstructive lung disease may retain CO_2 in their blood and normally have a mildly acidic pH. In these patients, it may be desirable to choose a reference pH value which is more acidic than 7.40. Persons of skill will readily appreciate clinical situations in which it is desirable to choose a reference pH value not equal to 7.40.

The elongate body will typically be a catheter assembly. The tubular elongate body may be constructed of a variety of materials. Generally, the elongate body will comprise a cross-linked polyolefin or halocarbon (usually fluorocarbon) polymer. Conveniently, the elongate body may be formed by extrusion of a suitable thermoplastic polymer by standard methods. Suitable materials for construction of the elongate body include nylons; cross-linked polyolefins such as polypropylenes, polyisoprenes, and polyethylenes; polyvinylchlorides; polyurethanes; halocarbon polymers (particularly fluorocarbons); and the like. Such materials display strong plastic memory and may be shaped to a desired diameter and shape when heated above their crystalline melting points. When the elongate tubular body is formed from a low strength material, such as a polyolefin, it will usually be desirable to provide a separate flexible reinforcement tube body to enhance the mechanical strength of the catheter.

The diameter and length of the elongate body are not critical and may vary. Generally, the outer diameter of the

catheter will be about 2 mm. The intended use of the catheter will determine the optimal diameter and length. Persons of skill are familiar with the optimal diameters and lengths for use in different applications of the catheters of the present invention.

The catheters may also be preformed to have different curved shapes which may facilitate percutaneous placement of the catheter into different body sites. The distal end of the elongate body will generally be placed within a body lumen while the proximal end of the elongate body will generally remain outside the body. Often, a radiopaque material may be applied to, or contained within, the elongate body to provide a means for fluoroscopic or radiographic localization of the elongate body following placement in a patient.

Typically, the catheter will be percutaneously inserted through a guide device, such as a Swan-Ganz catheter introducer. The catheter may also be inserted over guide wires. The length of the catheter may vary depending on the desired location of catheter placement and size of the patient. Generally, it will be desirable to monitor the pH in the central venous circulation, i.e., the superior vena cava, inferior vena cava, right atrium, right ventricle, and pulmonary arterial system. Therefore, the length of the catheter will need to be sufficiently long that the distal end of the catheter will reach the central venous circulation from the insertion site, generally about 10 to 75 cm.

By "proximal end", it is meant the end of the catheter left outside the body following percutaneous insertion. By "distal end", it is meant the end of the catheter which is in the body following percutaneous insertion.

The catheters will generally be tubular. The catheters may have a single lumen or multiple lumens. The lumens may be used to administer a medicament for the correction of blood pH. The lumens may also be used to administer physiological fluids, therapeutic or diagnostic compounds, nutritional compounds, or the like. Proximally,

the lumens will be terminated by a connector which provides a means for making a hermetic connection between the lumen and a fluid source, e.g., a Luer-lock connector. Distally, the lumens will terminate in at least one administration port. The administration ports will be located toward the distal end of the catheters.

A first pH sensor is located distally on the outer surface of the elongate body. The pH sensor will be capable of in vivo assessment of the pH of the blood. The sensor will generally be an ion sensitive field effect transistor (ISFET) sensor. A variety of commercially available pH sensors may be employed in the catheters of the present device, including micro-combination probes available from Microelectrodes, Inc., Londonderry, NH. The pH sensor may also include a pH electrode, reference electrode, electrolyte path, and current carrying wires between the electrodes. The catheter may have a first electrolyte lumen containing an electrolyte solution. The first electrolyte lumen terminates distally at a port near the first pH sensor and terminates proximally at the reference electrode. Wires carrying current between the pH electrode and the reference electrode will generally be contained within the wall of catheter.

Sensors for other physiological parameters that are suitable for in vivo use are also commercially available. These include, e.g., Na^+, K^+, Ca^{++}, pO_2, and pCO_2 available from, e.g., Microelectrodes, Inc. For ex vivo uses, flow-through electrodes for measurement of physiological parameters are also available from a variety of suppliers such as Microelectrodes, Inc. Generally such sensors will be ISFET sensors.

The administration ports may be located proximal or distal to the pH sensor on the elongate body. The relative placement of the administration port(s) and the pH sensor determines the mode of feedback control for administration of medicaments for normalizing pH. When the sensor is located upstream from the port in the circulation, the sensor will detect the systemic pH and respond accordingly. When the

sensor is located downstream from the port, the sensor will detect the pH of treated blood and respond accordingly.

The catheter may include a second pH sensor located in the elongate body. The second pH sensor may be located proximally or distally to the first pH sensor. Generally, the administration port(s) will be located between the first and second pH sensors on the elongate body. When a pH normalizing medicament is administered through the administration port, comparison of the value of the pH at the first pH sensor and the second pH sensor provides a means of determining the direction of blood flow around the distal catheter. Determining the direction of blood flow provides a means of determining the location of the distal end of the catheter. For example, following catheter placement in the internal jugular vein, if sodium bicarbonate is being infused through the administration port, the pH at the more distal pH sensor will be higher than the pH at the more proximal pH sensor when the distal end of the catheter is in the internal jugular vein, superior vena cava, right atrium, right ventricle, or pulmonary artery. The relative pH values may vary when the distal end of the catheter is in the right atrium. The blood pH at the more distal pH sensor will be lower than the pH at the more proximal pH sensor when the catheter is introduced through the internal jugular vein and advanced into the inferior vena cava. Therefore, comparison of the pH values provides a means for assessing the placement of the catheter and avoiding misplacement.

The catheter may also have a pCO_2 sensor located distally on the elongate body. The pCO_2 sensor provides a measure of the concentration of dissolved carbon dioxide in the blood. Knowledge of the blood pH and the blood pCO_2 provides a means to determine the complete acid base status of the patient and determine whether the patient requires increased ventilation or base correction. The respiratory and metabolic components of acidosis or alkalosis may be assessed by the Henderson-Hasselbach equation:

$$pH = pK + \log HCO_3^-/H_2CO_3,$$

as described in Lee (U.S. Patent No. 4,717,548, incorporated herein by reference). Acidosis beyond that caused by CO_2 has a metabolic cause, such as lactic acidosis from hypoperfusion or hypoxia.

In some embodiments of the present invention, the catheter may also have a balloon located distally on the catheter. A lumen will communicate with the interior of the balloon. Fluids may be introduced into the proximal end of the lumen for inflation of the balloon. Once inflated, the balloon can serve as a means to direct the catheter into the right heart by following the natural blood flow.

Also provided are devices for *in vivo* monitoring and directly and indirectly normalizing a value of a physiological parameter. The physiological parameter may include blood pH, blood pCO_2, blood pO_2, blood potassium concentration, blood calcium concentration, or the like. The devices generally comprise an *in vivo* means for sensing the value of the physiological parameter; a means for comparing the value of the physiological parameter to a reference value to produce a value difference; and a means for decreasing the magnitude of the value difference.

By "value" of a physiological parameter, it is meant a numerical representation of the physiological parameter.

The sensing means will generally be electronic. Electronic sensing means may be analog or digital. The sensing means may have a display for direct observation of the physiological parameter value by medical personnel. When the sensor is an electronic analog device, an analog/digital (A/D) converter may be used to convert the signal to digital form. Analog signals may also be amplified, prior to conversion by the A/D converter. Representative pH and pCO_2 sensors are described above.

Devices of the present invention also include a means for comparing the physiological parameter value to a reference value. The reference value will be stored in the comparing means. The comparing means will generally be electronic and may operate in analog or digital mode. Often the comparing means will be a microprocessor. The

microprocessor may also provide a real time display of the value of the measured physiological parameter to provide medical personnel with clinical data to aid in patient management. The microprocessor may also store selected values of the measured physiological parameter as a means of recording the patient's clinical condition. When analog signals are compared, the reference value will generally be a voltage range. The comparing means may also be a hard wired circuit as described below.

The reference value is preselected and generally be within the normal physiological range of the physiological parameter, e.g., a digital pH range of 7.35-7.45. The clinician may also adjust the reference for appropriate clinical settings. For example, it is generally advisable to keep potassium concentration at low normal or minimally subnormal when coming off cardio-pulmonary bypass. In this instance the clinician could select a reference value which may be just below the normal range. Persons of skill may readily select reference values by methods well known in the medical art.

The comparing means will compare the difference between the measured value and the reference value to produce a value difference. The value difference is representative of the variation of the physiological parameter from normal. The value difference may be positive or negative.

A means for decreasing the magnitude of the value difference is also included in the present invention. The value difference decreasing means provides a treatment to the patient so that the magnitude of the value difference will move toward zero. In some clinical settings the value difference decreasing means will not actually decrease the magnitude of the value difference, but will stabilize or slow the rate of increase of the magnitude of the value difference. In these instances, it can be seen that while the value decreasing means is not normalizing the value of the physiological parameter, it is stabilizing or slowing the variation of the physiological parameter value.

The value decreasing means will vary with the use of the device. The value decreasing means may be an infusion pump which can provide a controlled quantity of a physiological normalizer. By "physiological normalizer," it is meant a substance which will have the effect of normalizing the value of a physiological parameter when administered to a patient. For example, a solution of sodium bicarbonate may be a physiological normalizer which can be administered intravenously to at least partially correct acidosis. A solution of potassium chloride may be used as a physiological normalizer for the correction of hypokalemia. Increased ventilation of the lungs may provide a mixture of gasses (or pure gas) as a physiological normalizer to correct respiratory acidosis. Other examples of physiological normalizers are well known in the art.

The infusion pump will typically be a variable speed pump. The speed of the infusion pump will determine the dosage of physiological normalizing solution provided to the patient. The speed may be controlled by altering the voltage provided to the pump or by directly controlling the speed of the pump motor.

In some embodiments of the present invention the value decreasing means may be a gas mixer. When the pO_2 of the blood is the measured physiological parameter, altering the fraction of O_2 in the inspired gas can alter the value of the blood pO_2 and function to normalize the value. Blood pCO_2 may be normalized by varying the respiratory rate or inspiratory tidal volume of patients receiving ventilatory support. In these embodiments, the value decreasing means will generally be a means to alter ventilator controls.

Some embodiments of the present invention comprise a tubular elongate body having a proximal end, a distal end, and a wall defining an interior region and an exterior region of the elongate body; a first pH sensor located distally on the exterior wall of the elongate body; a port located distally on the elongate body, which port provides a fluid opening between the interior region and the exterior region of the elongate body; a first pH sensor linkage connecting the sensor to a

signal analyzer; and an analyzer linkage connecting the signal analyzer to a means for normalizing the pH.

A sensor as described above is located distally on the elongate body. By placing the distal end of the elongate body in a desired location in the body, the sensor can be placed relatively precisely. The sensor generates sensor signals which represent the value of the measured physiological parameter. The sensor is connected to a sensor linkage which will carry sensor signals representing the value of the physiological parameter which are generated by the sensor. Typically, the sensor signals will be electrical and the sensor linkage will be a wire. The sensor signals may also be light, such as collected reflectance from an O_2 sensor. In this case the sensor linkage will generally be a fiber optic strand. The sensor linkage may also be a transmitter which does not require physical linkage to transfer sensor signals generated by the sensor.

The sensor signals are transferred to a signal analyzer which is connected to the sensor linkage. The signal analyzer receives the sensor signals from the sensor and compares the sensor signals to a pre-selected reference value stored in the signal analyzer. The signal analyzer may also display the sensor signal or store the sensor signal. The signal analyzer will typically be a microprocessor. Alternatively, the signal analyzer may be a hard wired circuit that is constructed to perform the functions of the signal analyzer (e.g., Fig. 8).

In one embodiment of a hard wired circuit, the pH meter produces a voltage signal that represents the pH of the blood. The voltage signal passes through a buffer amplifier isolating the controller circuitry from the pH meter and amplifying the signal to a usable level. An adjustable voltage signal representing the target pH is produced by a potentiometer. The blood pH signal and the target pH signal are summed by a summing amplifier. When the blood pH signal equals the target pH signal, the output of the summing amplifier equals zero volts. The greater the difference between the blood pH and the target pH, the greater the

magnitude of the output of the summing amplifier. The voltage signal from the summing amplifier is amplified by an adjustable gain amplifier. Adjustment of the gain of the amplifier allows for adjustment of the speed of the response of the system (ultimately the infusion pump) to a given detected blood pH abnormality. The voltage from the amplifier is converted to a frequency signal by a voltage to frequency converter. Higher voltage output from the amplifier results in conversion to a higher frequency by the signal converter. The frequency signal from the converter is generally a TTL compatible signal (digital) that is passed through a digital buffer for isolation between the controller and a stepping motor that controls the rate of medicament infusion.

The signal analyzer produces an analyzer signal which represents the difference between the sensor signal and the reference value. The analyzer signal is transmitted to a means for normalizing the physiological parameter. The analyzer signal provides an input to the normalizing means. In response to the input, the normalizing means will provide a therapeutic response to the patient as described above. Generally, the normalizing means will comprise a microprocessor for comparing the signal to a reference value and an infusion pump driven by the microprocessor. The infusion pump will provide an amount of therapeutic medicament determined by the microprocessor. Alternatively, the normalizing means may comprise a hard wired circuit instead of a microprocessor, or a method to control ventilatory parameters, e.g., F_iO_2, respiratory rate, tidal volume, and the like, instead of an infusion pump.

In some embodiments of the present invention, the devices may monitor and normalize both blood pH and blood pCO_2. These devices include a pH sensor and a pCO_2 sensor which are placed in the patient's body. Generally, the signals produced by the pH sensor and the pCO_2 sensor will be transmitted to a microprocessor. The microprocessor will determine the respiratory and metabolic components of any acid-base disturbances. The microprocessor may then control a variety of infusion pumps which could administer a

physiologically acceptable base to correct metabolic acidosis or a physiologically acceptable acid to correct metabolic alkalosis. The microprocessor may also control ventilatory regulators for persons requiring ventilatory support. The microprocessor may adjust the respiratory rate, tidal volume, or both to alter the pCO_2 of the blood and correct any component of respiratory acidosis or alkalosis.

The devices of the present invention may also include sensors which monitor the end expiratory pCO_2 of patients on ventilatory support. Such monitoring is useful in a variety of disease states, including chronic obstructive pulmonary disease, drug overdose, post-operative respiratory depression, and the like. The end expiratory pCO_2 closely approximates the arterial blood pCO_2. The signal from the end expiratory pCO_2 sensor may be transmitted to a microprocessor (or appropriate hard wired device) and provide the information needed for controlling ventilatory parameters, such as FiO_2, tidal volume, or respiratory rate. Typically, the end expiratory pCO_2 sensor will be placed at the junction of an endotracheal tube (or tracheostomy appliance) and ventilator tubing.

The end expiratory pCO_2 sensor may be used in conjunction with intravascular catheters which monitor pH. The signals are generally transmitted to a single microprocessor. The microprocessor may then determine and normalize metabolic and respiratory acid-base disturbances as described above.

The present invention also provides devices for *ex vivo* monitoring and normalizing a value of a physiological parameter in a patient. A wide variety of parameters may be measured, e.g., pH, pO_2, pCO_2, potassium concentration, calcium concentration, and the like. These devices are particularly useful in cardio-pulmonary bypass, but may also be used in other therapeutic procedures, such as potassium monitoring during cardio-pulmonary bypass or calcium monitoring during platelet phoresis or dialysis, and the like.

Generally, the devices useful in *ex vivo* monitoring will comprise a flow-through tube having a lumen containing a

sensor, which sensor is capable of producing a sensor signal representing the value of the physiological parameter; a sensor linkage connecting the sensor to a signal analyzer; and an analyzer linkage connecting the signal analyzer to a means for normalizing the physiological parameter. The components of this embodiment of the present invention are similar to those described above for *in vivo* monitoring. Alternatively, the device may comprise an elongate body having a proximal end and a distal end; a sensor located distally on the elongate body, which sensor is capable of producing a sensor signal representing the value of the physiological parameter; a sensor linkage connecting the sensor to a signal analyzer; and an analyzer linkage connecting the signal analyzer to a means for directly and indirectly normalizing the physiological parameter.

The *ex vivo* device will be placed in a body fluid, generally blood, from a patient which is being treated *ex vivo*. The sensor may detect a variety of physiological parameters, such as pH, pCO_2, calcium concentration, potassium concentration, and the like. The device, whether flow-through or an elongate body, will generally be hermetically sealed in the flow path of the body fluid. The sensors will generally be located downstream from the *ex vivo* therapy device.

In embodiments comprising an elongate body, the body will often be tubular so that the lumen may carry a therapeutic medicament to normalize the physiological parameter. The lumen will terminate distally in at least one port. The port may be located proximal or distal to the sensor. In some embodiments of the present invention, the elongate body may have multiple lumens which may be used to deliver different medicaments. For other embodiments of *ex vivo* devices, normalization will generally occur by another means, e.g., downstream infusion of a medicament, and the like.

The present invention also provides methods for *in vivo* monitoring and normalizing a value of a physiological blood parameter. The methods generally comprise inserting the distal end of the elongate body of *in vivo* monitoring devices,

as described above, into a blood vessel of a patient; and supplying a physiological normalizer to the normalizing means of the device. The device will then monitor the blood parameter and automatically supply the appropriate physiological normalizer as described above.

Referring to Fig. 1, a catheter 10 of the claimed invention is demonstrated. The elongate body 12 contains a single lumen 14. Distally, the lumen 14 terminates in multiple ports 16. A pH sensor 18 is located distal to the ports 16 on the catheter 10. A wire 20 extends proximally from the pH sensor 18 to an electronic connector 22. The electronic connector 22 provides a means for transmitting signals from the pH sensor 18 to a means for analyzing the signal. Proximally, the lumen 14 terminates a in fluid connector 24. The fluid connector 24 extends hermetically into the proximal end of the lumen 14. The fluid connector 24 includes a proximal Luer-lock hub for fluidly connecting to an infusion pump. Fig. 2 illustrates a catheter 10 of the present invention in which the ports 16 are located distal to the pH sensor 18.

Fig. 3 illustrates a catheter 10 of the present invention having two lumens 14, 15. One lumen 14 terminates distally in multiple ports 16. The other lumen 15 terminates distally in a single port 17. A pH sensor is located between the ports 16 and 17 on the elongate body 12. The lumens terminate proximally in fluid connectors 24 as described above.

Fig. 4 illustrates a catheter 10 of the present invention. The catheter has a first pH sensor 18 located distal to the ports 16 on the elongate body 10. A second pH sensor 19 is located proximal to the ports 16 on the elongate body 10. Wires 20, 21 transmit signals from the pH sensors 18, 19 to a signal analyzer. Electronic connectors 22,23 are located at the proximal end of the wires 20, 21.

Fig. 5 illustrates a catheter 10 of the present invention. The catheter 10 has a pH sensor 18 and a pCO_2 sensor 25. The catheter 10 also has two lumens 14, 15 for delivery of therapeutic medicaments.

Fig. 6 illustrates a device 30 of the present invention. A catheter 32 is in the right heart of a patient 34. A sensor on the catheter 32 transmits signals representing a physiological parameter through wires 36 to a microprocessor 38. The microprocessor 38 analyzes the signal and compares the signal to a reference value. The microprocessor 38 transmits a normalizing signal through an electronic connector 40 to an infusion pump 42. The normalizing signal controls the speed of the infusion pump 42. The infusion pump 42 delivers a normalizing fluid from a reservoir 44 to the patient 34 through a lumen in the catheter 32. Hence, the amount of normalizing fluid delivered to the patient 34 is determined by the value of the physiological variable measured in the patient 34.

Fig. 7 illustrates a device of the present invention for monitoring and normalizing the blood pCO_2 in a patient 34. A catheter 32 is located in the right heart of the patient 34. The catheter 32 has a distally-located pCO_2 sensor. The sensor produces a signal which is transmitted to a microprocessor 38. The microprocessor 38 analyzes the signal and sends a normalizing signal to a ventilator 50. The normalizing signal controls the respiratory rate of the ventilator 50. Therefore, abnormal changes in the blood pCO_2 of a patient 34 may be normalized.

Fig. 8 illustrates a typical hardwired circuit for control of blood pH by a device of the present invention. A pH meter produces a voltage signal 100 that represents the pH of the blood. The voltage signal 100 passes through a buffer amplifier 102 isolating the controller circuitry from the pH meter and amplifying the signal to a usable level. An adjustable voltage signal representing the target pH is produced by a potentiometer 104. The blood pH signal and the target pH signal are summed by a summing amplifier 106. When the blood pH signal equals the target pH signal, the output of the summing amplifier 106 equals zero volts. The greater the difference between the blood pH and the target pH, the greater the magnitude of the output of the summing amplifier 106. The voltage signal from the summing amplifier 106 is amplified by

an adjustable gain amplifier 108. Adjustment of the gain of the amplifier 108 allows for adjustment of the speed of the response of the system (ultimately the infusion pump) to a given detected blood pH abnormality. The voltage from the amplifier 108 is converted to a frequency signal by a voltage to frequency converter 110. Higher voltage output from the amplifier 108 results in conversion to a higher frequency by the frequency converter 110. The frequency signal from the converter 110 is generally a TTL compatible signal (digital) that is passed through a digital buffer 112 for isolation between the controller and a stepping motor that controls the rate of medicament infusion.

Figs. 9A-9F illustrate different embodiments of the distal portions of elongate bodies of the present invention. Fig. 9A demonstrates a device having one pH sensor 18 located distal to a plurality of ports 16. Such a device senses the pH of treated blood. The device may correct a combined acidosis, detect proper placement by determining the direction of blood flow, and/or allow calculation of cardiac output by a discrete bolus injections of a base or acid.

Cardiac outputs may be determined by the following formula:

$$C.O. = \frac{V_I (pH_B - pH_I)\ (60)\ (1+C)}{\int_0^\infty \Delta pH_B(t)\, dt}$$

Where,

C.O.	=	Cardiac output (ℓ/min)
V_I	=	Injectate volume (ℓ)
pH_B	=	Blood pH
pH_I	=	Injectate pH
$\int_0^\infty \Delta pH_B(t)\,dt$	=	area under the time-pH curve in (pH - sec)
C	=	Correction factor for blood buffering of pH_I.

Fig. 9B illustrates a device having a pH sensor 18 located proximal to the a plurality of ports 16. This device detects the pH of untreated blood and may be used to correct combined acidosis.

Fig. 9C illustrates a device having a pH sensor 18 and a pCO_2 sensor 25 located distal to a plurality of ports 16. This device may be used to separately correct metabolic and respiratory components of acidosis. Placing the pH sensor 18 and pCO_2 sensor 25 proximal to the ports 16 (Fig. 9D) also allows for separate and simultaneous correction of metabolic and respiratory components of acidosis.

Figs. 9E and 9F illustrate devices having pH sensors 18 alone (Fig. 9E) or with pCO_2 sensors 25 (Fig. 9F) located both proximal and distal to the ports 16. These devices provide a means for accurately correcting acidosis even if the catheter is improperly positioned. Cardiac output may be measured continuously by determining the pH difference between the upstream and downstream pH sensors in response to administration of a known amount of acid or base as described above. The device of Fig. 9E having pH sensors 18 alone may correct combined acidosis. The device of Fig. 9F with both pH sensors 18 and pCO_2 sensors 25 may independently correct respiratory and metabolic acidosis components.

Fig. 10 illustrates a flow-through device of the present invention for *ex vivo* use. Blood flows through a lumen 60 past a pH sensor 18 and pCO_2 sensor 25 and ports 16. The pH sensor 18 and pCO_2 sensor 25 may be located upstream or downstream of the ports 16.

All publications and patents mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication or patent was specifically and individually indicated to be incorporated herein by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the claims.

WHAT IS CLAIMED IS:

1. A catheter for monitoring and normalizing blood pH, comprising:

a tubular elongate body having a proximal end, a distal end, and a wall defining an interior region and an exterior region of the elongate body;

a first pH sensor located distally on the exterior wall of the elongate body; and

a port located distally on the elongate body, which port provides a fluid opening between the interior region and the exterior region of the elongate body.

2. A catheter as in claim 1, wherein the first pH sensor is located distal to the port on the elongate body.

3. A catheter as in claim 1, wherein the port is located distal to the first pH sensor on the elongate body.

4. A catheter as in claim 1, further comprising a second pH sensor, whereby the port is located between the first pH sensor and the second pH sensor on the elongate body.

5. A catheter as in claim 1, further comprising a connector located proximally on the elongate body, which connector provides a fluid connection between the interior region of the elongate body and a fluid source.

6. A catheter as in claim 5, wherein the connector is a Luer-lock connector.

7. A catheter as in claim 1, further comprising a first pCO_2 sensor located distally on the wall of the elongate body.

8. A catheter as in claim 7, further comprising a second pCO_2 sensor, wherein the first pCO_2 sensor is located proximal to the port and the second pCO_2 sensor is located distal to the port.

9. A catheter as in claim 1, further comprising a balloon located distally on the exterior surface of the wall of the elongate body, which balloon is fluidly connected to an inflation lumen.

10. A device for *in vivo* monitoring and normalizing a value of a physiological parameter, comprising:

an *in vivo* means for sensing the value of the physiological parameter;

a means for comparing the value of the physiological parameter to a reference value to produce a value difference; and

a means for decreasing the magnitude of the value difference.

11. A device of claim 10, wherein the physiological parameter is blood pH, blood oxygen concentration, blood carbon dioxide concentration, blood potassium concentration, blood sodium concentration, blood glucose concentration, blood calcium concentration, or blood magnesium concentration.

12. A device of claim 11, wherein the sensing means comprises a ISFET sensor.

13. A device of claim 10, wherein the comparing means comprises a microprocessor.

14. A device of claim 13, wherein microprocessor stores selected measured values of the physiological parameter.

15. A device of claim 13, wherein the microprocessor provides a real time display of the value of the physiological parameter.

16. A device of claim 10, wherein the comparing means comprises a summing amplifier.

17. A device of claim 10, wherein the value difference decreasing means comprises a variable speed infusion pump.

18. A device for *in vivo* monitoring and normalizing blood pH in a patient, comprising:

a catheter as in claim 1;

a sensor linkage connecting the first pH sensor to a signal analyzer; and

an analyzer linkage connecting the signal analyzer to a means for normalizing the physiological parameter.

19. A device as in claim 18, wherein the normalizing means comprises an infusion pump.

20. A device as in claim 18, wherein the normalizing means comprises a gas source capable of altering the F_iO_2 of the gas, a means of controlling the respiratory rate of a ventilator, or a means of controlling the tidal volume of a ventilator.

21. A device as in claim 18, further comprising a pCO_2 sensor or pO_2 sensor located distally on the elongate body.

23. A device as in claim 18, wherein the signal analyzer is a microprocessor.

24. A device for *ex vivo* monitoring and normalizing a value of a physiological parameter in a patient, comprising:

a lumen containing a sensor, which sensor is capable of producing a sensor signal representing the value of the physiological parameter;

a sensor linkage connecting the sensor to a signal analyzer; and

an analyzer linkage connecting the signal analyzer to a means for normalizing the physiological parameter.

25. A device as in claim 24, wherein the elongate body further comprises a means for hermetic connection to a blood conduit in a cardio-pulmonary bypass machine.

26. A device as in claim 24, wherein the physiological parameter is blood pH, blood pO_2, or blood pCO_2.

27. A method for *in vivo* monitoring and normalizing a value of a physiological blood parameter, comprising:

inserting the distal end of the elongate body of a device as in claim 17 into a blood vessel; and

supplying a physiological normalizer to the normalizing means of the device.

28. A method as in claim 27, wherein the physiological parameter is blood pH and the physiological normalizer is sodium bicarbonate.

29. A method as in claim 27, wherein the physiological parameter is blood pO_2 and the physiological normalizer is ventilation.

30. A method as in claim 27, wherein the blood vessel is an artery.

31. A method as in claim 27, wherein the blood vessel is a vein.

32. A method as in claim 27, wherein the blood vessel is a cardiac chamber.

33. A method for *ex vivo* monitoring and normalizing a value of a physiological parameter during cardio-pulmonary bypass, comprising:

joining a device as in claim 24 with a blood conduit of a cardio-pulmonary bypass machine; and

supplying a physiological normalizer to the normalizing means of the device.

34. A method as in claim 33, wherein the physiological parameter is blood pH, blood pO_2, or blood pCO_2.

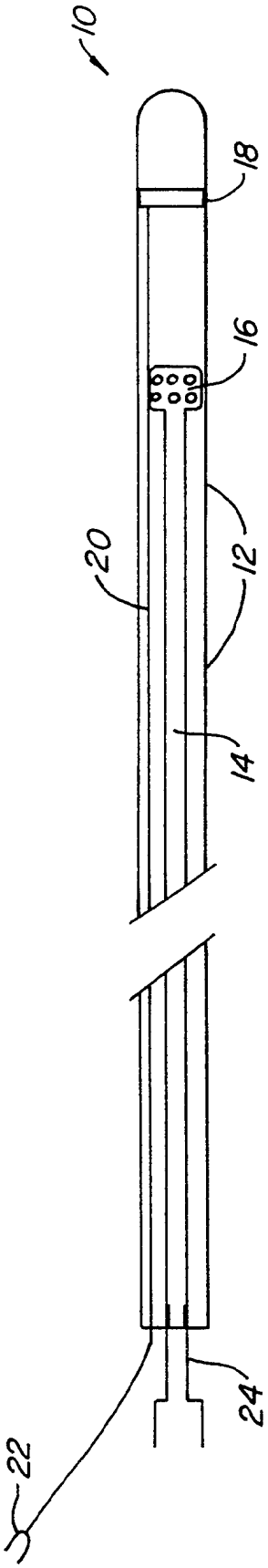

FIG. 1.

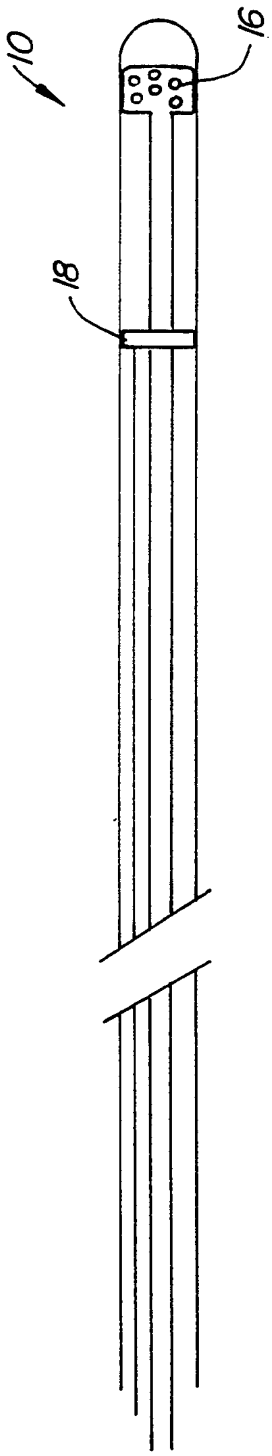

FIG. 2.

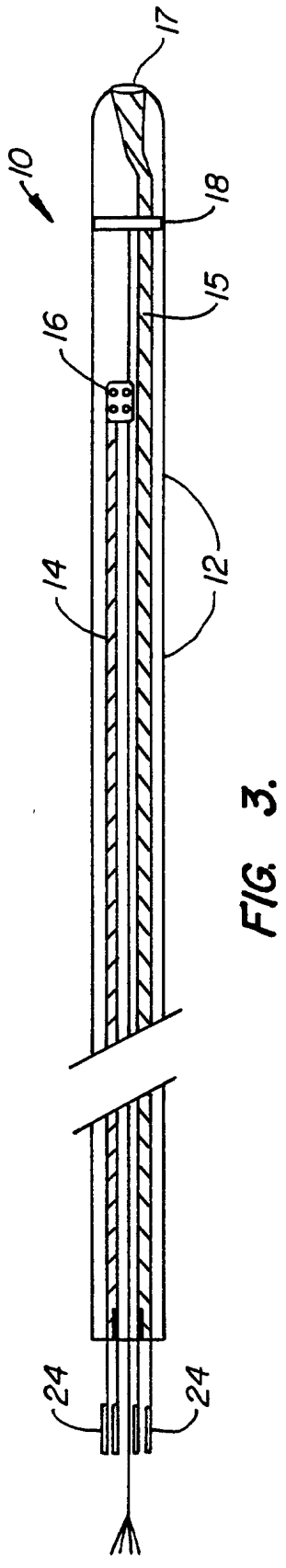

FIG. 3.

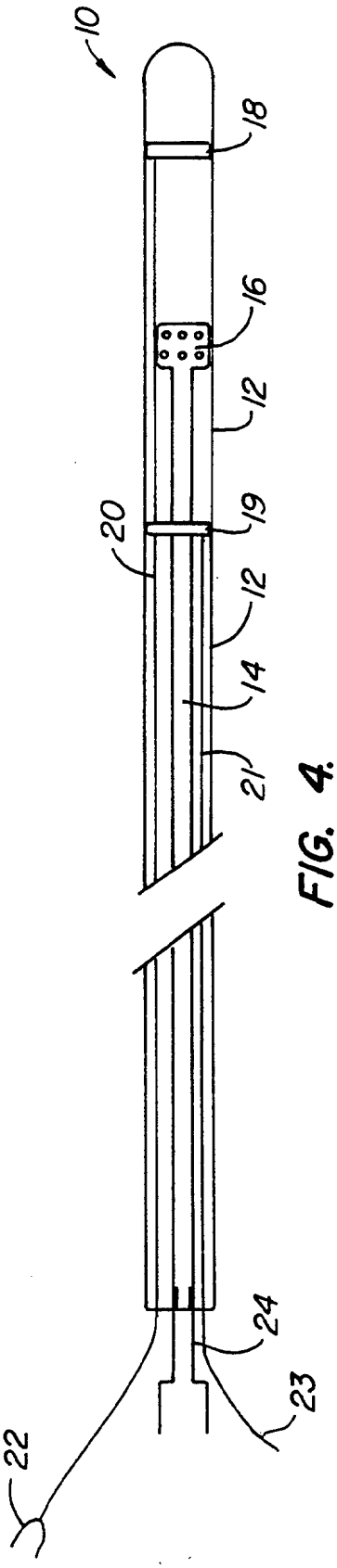

FIG. 4.

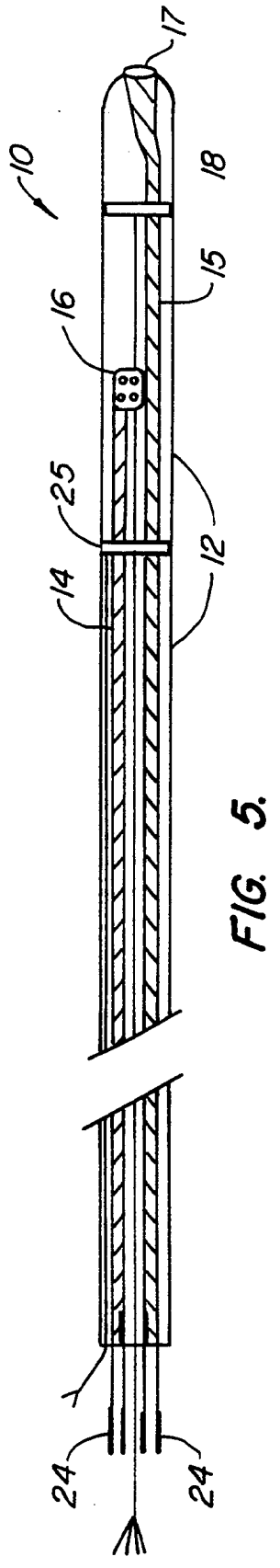

FIG. 5.

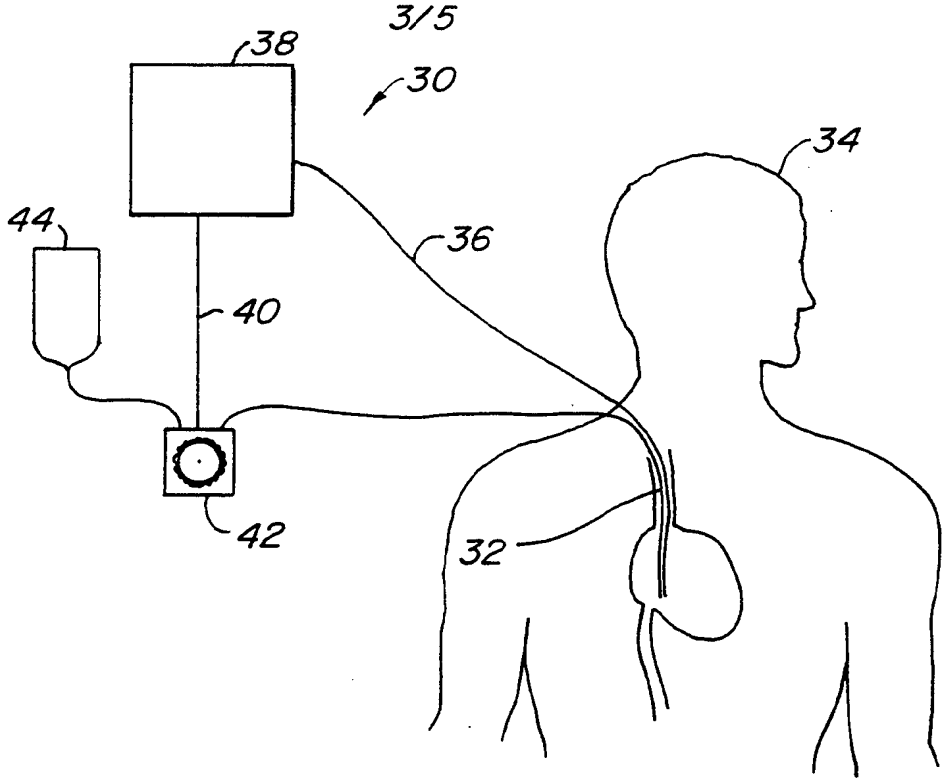

FIG. 6.

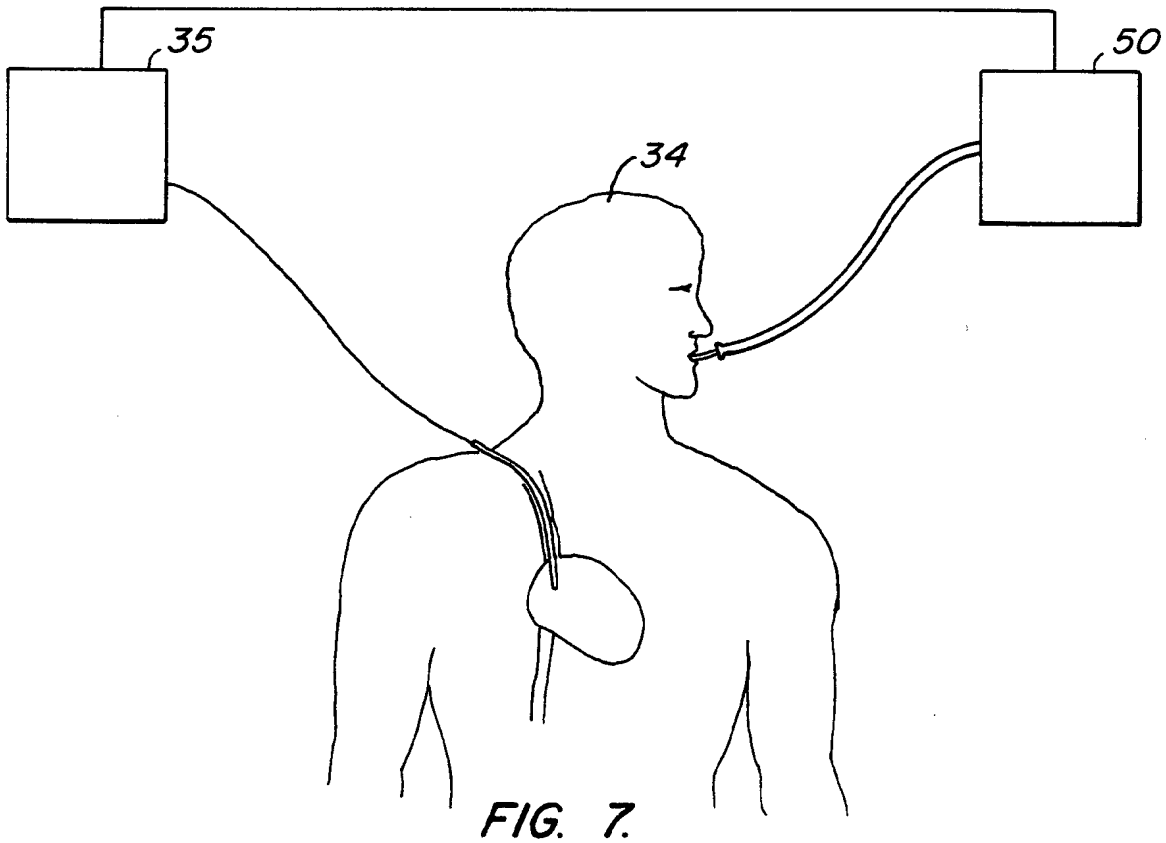

FIG. 7.

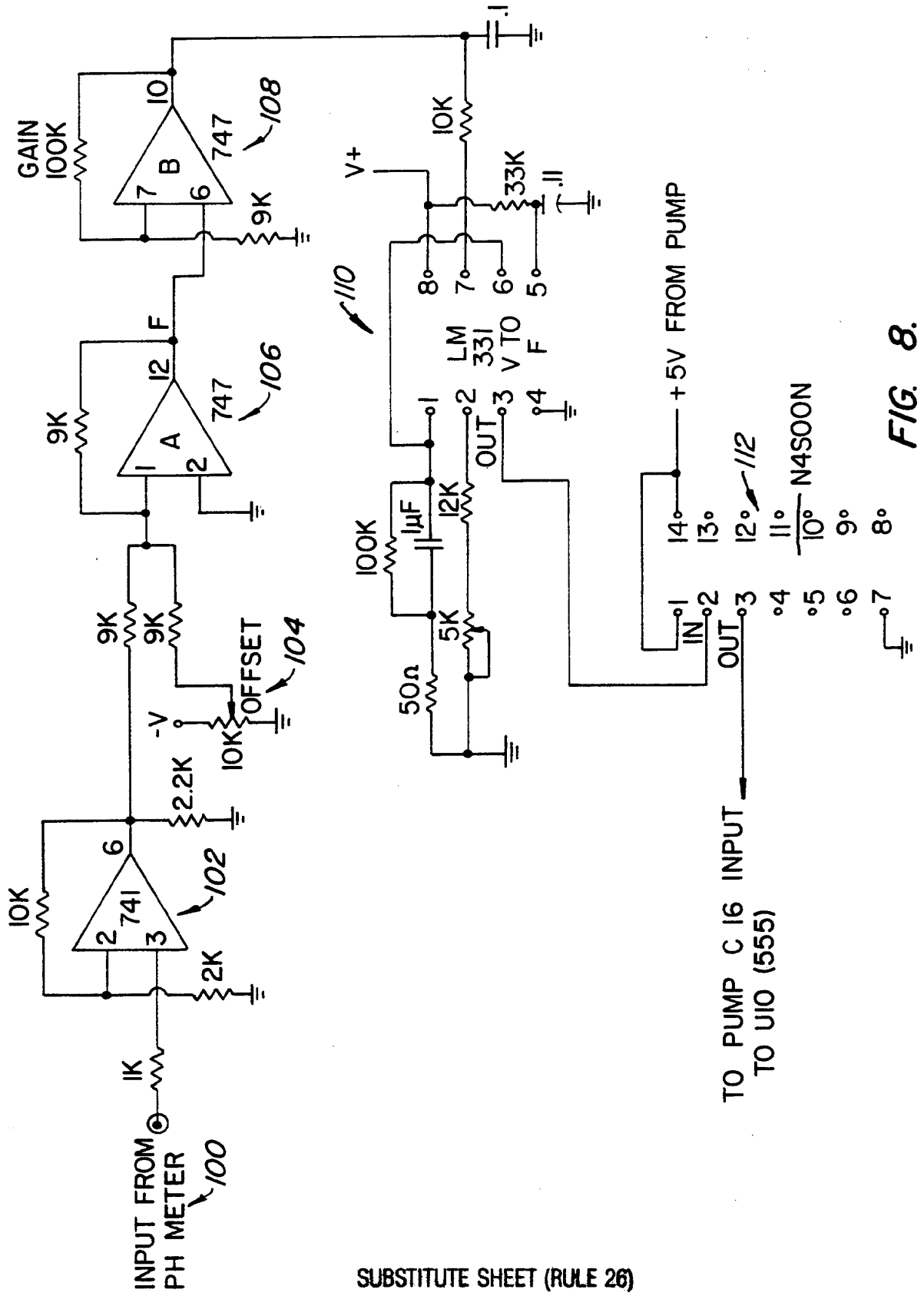
INPUT FROM PH METER
100
1K
10K
741
102
2K
2.2K
-V
10K
OFFSET
104
9K
9K
9K
A
747
106
F
12
1
2
9K
GAIN 100K
B
747
108
10
7
6
9K
.1
10K
V+
33K
.11
110
8
7
6
5
LM 331 V TO F
1
2
OUT
3
4
100K
1μF
12K
5K
50Ω
+5V FROM PUMP
14
13
12
11
10
9
8
IN
OUT
1
2
3
4
5
6
7
112
N4SOON
TO PUMP C 16 INPUT
TO U10 (555)

FIG. 8.

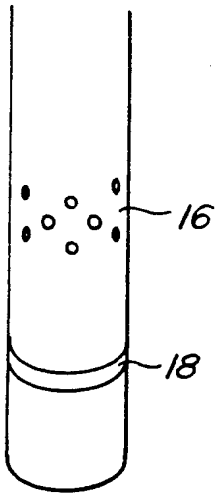

FIG. 9A.

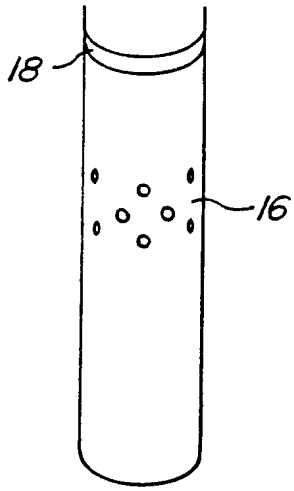

FIG. 9B.

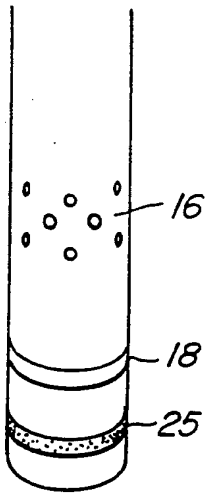

FIG. 9C.

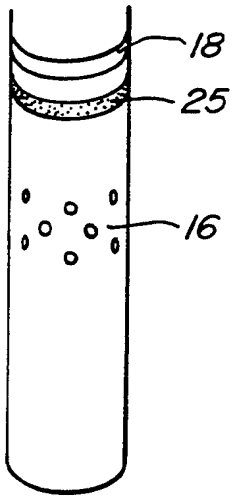

FIG. 9D.

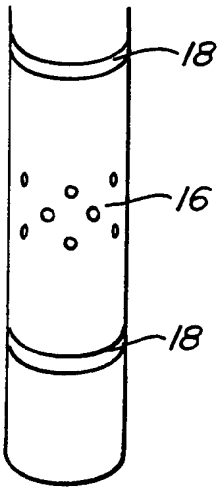

FIG. 9E.

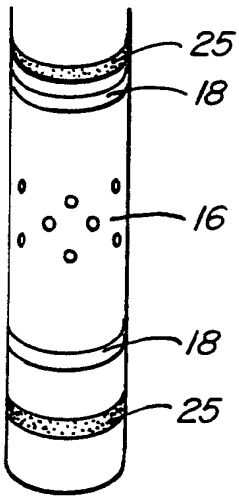

FIG. 9F.

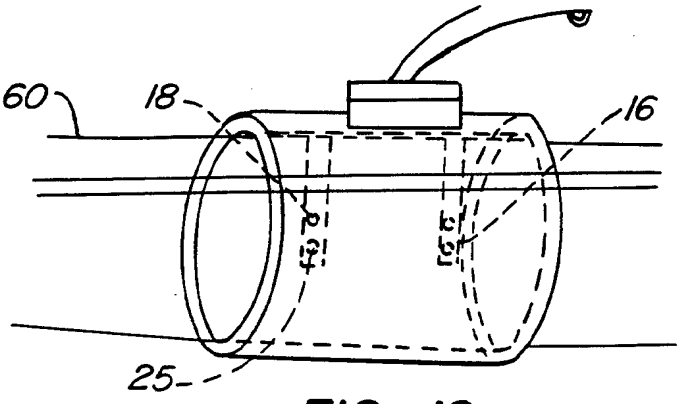

FIG. 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11618

A. **CLASSIFICATION OF SUBJECT MATTER**
IPC(6) :A61B 05/00
US CL :128/635
According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/635; 604/50, 65-67; DIGEST 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,981,470, (BOMBECK, IV), 01 January 1991. See entire document.	1-3, 5, 6. 9 ----- ---------- 4, 7, 8
A	US, A, 4,151,845, (CLEMENS), 01 May 1979. See entire document.	1-32
Y	BIO-MED SCIENCES INSTRUMENTATION, SIXTH NATIONAL SYMPOSIUM, May 21-23, 1968; "A System for Monitoring Pulmonary Ventilation," (JOHNS ET AL.). See pages 119-121.	21, 29

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 JANUARY 1995	Date of mailing of the international search report 27 MAR 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Stacia Sinnik for ROBERT NASSER Telephone No. (703) 308-3251

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11618

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 4,633,878, (BOMBARDIERI), 06 January 1987. See entire document.	10, 11, 13-17, 27, 30-32 ---------- 12, 28, 29
X --- Y	US, A, 4,717,548, (LEE), 05 January 1988. See entire document.	24-26 ----------7, 8, 28
Y	US, A, 5,002,055, (MERKI ET AL.), 26 March 1991. See entire document.	4, 8, 18-21, 23
Y	EP, A, 0,036,171, (BERGVELD ET AL.), 23 Septemebr 1981. See entire document.	18-21, 23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11618

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/11618

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

Species I, drawn to Figs. 1-9.

Species II, drawn to Fig. 10.

The claims are deemed to correspond to the species listed above in the following manner:
Claims 1-23 and 27-32 are drawn to Species I.

Claims 24-26 are drawn to Species II.

The following claims are generic: none.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

Species I is drawn to an in vi-vo measurement system.

Species II is drawn to an ex-vi-vo system.